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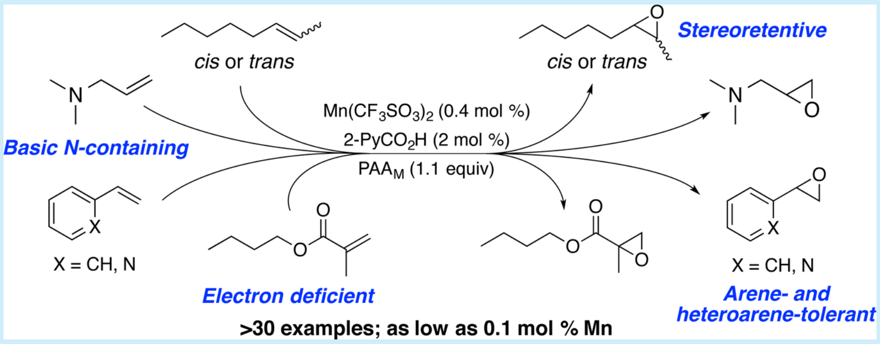
Manganese(II)/Picolinic Acid Catalyst System for Epoxidation of Olefins

Ross A. Moretti, J. Du Bois, and T. Daniel P. Stack*

Department of Chemistry, Stanford University, Stanford, California 94305, United States

Supporting Information

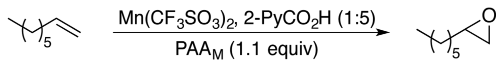


ABSTRACT: An in situ generated catalyst system based on $Mn(CF_3SO_3)_2$, picolinic acid, and peracetic acid converts an extensive scope of olefins to their epoxides at 0 °C in <5 min, with remarkable oxidant efficiency and no evidence of radical behavior. Competition experiments indicate an electrophilic active oxidant, proposed to be a high-valent Mn = O species. Ligand exploration suggests a general ligand sphere motif contributes to effective oxidation. The method is underscored by its simplicity and use of inexpensive reagents to quickly access high value-added products.

Epoxides are a widely used class of compounds, valued as intermediates to a range of chemical functionality.[1] The selective production of epoxides from abundant olefin starting materials has therefore received much attention over the past several decades. Transition metal catalysts have been key to the development of many of these methodologies, yet a general method for epoxidation of alkenes of diverse steric and electronic profiles does not exist. Established catalysts in the field, such as methyltrioxorhenium[2] and metal−salen complexes,[3] are limited in scope and not broadly useful for substrates more electron-deficient than a terminal olefin. Recent advances have derived inspiration from oxidative metalloenzymes,[4] pursuing Fe- and Mn-based catalysts that use environmentally benign terminal oxidants, such as H_2O_2 and peracetic acid (PAA).[5] This class of catalysts is more powerful than its predecessors, but poor selectivity and ligand oxidation[6] are observed as undesired consequences. Elaborate ligand scaffolds[7] have been designed to modulate reactivity, but such synthetically laborious modifications may limit their widespread use. We report herein a *general* epoxidation catalyst system, capable of transforming alkenes of varied geometric and electronic natures to their epoxides with good selectivity and high oxidant efficiency. Furthermore, the transformation is achieved using the simple, inexpensive reagents $Mn(CF_3SO_3)_2$, picolinic acid ($2\text{-}PyCO_2H$), and PAA, making it a readily accessible choice for epoxidation.

Epoxidation was first investigated using 1-octene as a model substrate. Optimization of reaction conditions achieved complete conversion within minutes at subambient temperatures using 1.1 equiv of a base-modified commercial PAA solution (PAA_M; see the Supporting Information). We selected the conditions of 0.4 mol % of $Mn(CF_3SO_3)_2$ and 2 mol % of $2\text{-}PyCO_2H$ at 0 °C over 5 min, with slow addition of PAA_M (Table 1, entry 1), to be our general working conditions due to their broad applicability and ease of execution. Lower alkene

Table 1. Epoxidation of 1-Octene with Mn/$2\text{-}PyCO_2H$ Catalyst System[a]



	Mn (mol %)	[alkene] (M)	temp (°C)	conv (%)	yield (selectivity) (%)
1[b]	0.4	0.45	0	98	83 (85)
2[c]	0.4	0.1	0	95	80 (84)
3[b]	0.1	0.45	0	93	80 (86)
4[d]	0.4	0.45	−40	96	85 (89)
5[e]	0.4	0.45	−78	90	82 (91)
6	none	0.45	0	<5	trace

[a] Conversion and yield determined by GC relative to dodecane internal standard. Results are an average of three trials: conversion ±2%, yield ±1%. Selectivity = (yield/conversion) × 100. PAA_M = 10:3:13 (v/v/v) 32% PAA/10% KOH (aq)/AcOH. [b] MeCN, 5 min. [c] MeCN, 10 min. [d] MeCN, 20 min. [e] 1:1 EtCN/*i*PrCN (v/v), 30 min.

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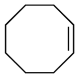
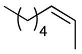
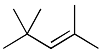
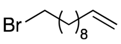
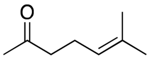
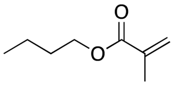
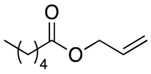
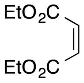
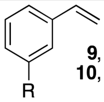
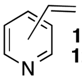
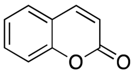
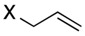
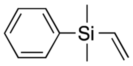
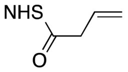
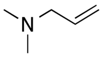
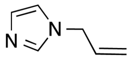
Table 2. Scope of Epoxidation with Mn/2-PyCO$_2$H Catalyst System[a]

	substrate	conversion (%)	yield (selectivity)(%)
1		100	99 (99)
2		99	91[b] (92)
3		95	83 (87)
4		91	81 (91)
5		98	87 (89)
6		89	82 (92)
7		86	77 (90); 76[c]
8		20 45[d]	10 (50) 19[e] (45)
9	 **9**, R = H	77	61[f] (80)
10	**10**, R = NO$_2$	91	85[g] (92)
11	 **11**, 2-vinyl	87	80 (92)
12	**12**, 4-vinyl	85	77 (90)
13		88	78 (89); 72[c]
14	 **14**, X = Cl	100	75 (75)
15	**15**, X = Br	100	77 (77)
16		71	50 (70)
17		100	69 (69); 64[c]
18[h]		100	68 (68)
19[h]		52 62[i]	49 (94) 59 (95); 52[c]

[a] 0.4 mol % of Mn(CF$_3$SO$_3$)$_2$, 2 mol % of 2-PyCO$_2$H, 100 μmol of substrate in MeCN (0.45 M), 1.1 equiv of PAA$_M$, 0 °C, 5 min. Conversion and yield determined by GC and ^{1}H NMR relative to an internal standard (see the Supporting Information). Results are an average of three trials: conversion ±2%, yield ±1%. [b] *cis*-Epoxide produced selectively. [c] Isolated yield. [d] 4.0 equiv of PAA$_M$, 10 min. [e] 4% *trans*-epoxide observed as byproduct; competing ester cleavage also observed. [f] 14% phenylacetaldehyde observed as byproduct. [g] 5% 3-nitrophenylacetaldehyde observed as byproduct. [h] With 1 equiv BF$_3$·MeCN in 1:1 EtCN/*i*PrCN (v/v), −78 °C, 30 min. [i] 1.5 equiv of PAA$_M$.

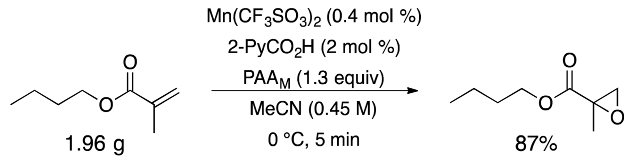
concentrations and catalyst loadings (Table 1, entries 2 and 3), as well as alternative Mn(II) salts (e.g., MnCl$_2$, Mn(OAc)$_2$), can be equally effective. Surprisingly, epoxidation is attainable at temperatures as low as −78 °C[8] (Table 1, entries 4 and 5), and selectivity increases with decreasing temperature. The indicated 1:5 ratio of Mn(II) salt to 2-PyCO$_2$H is rationalized using the binding equilibria for Mn(II) and 2-PyCO$_2$H.[9] For the concentrations of species in this study, a 1:5 ratio maximizes formation of the bis-ligated species in solution (see the Supporting Information), a ligand sphere comparable to many known Mn and Fe oxidation catalysts.[5]

The selected conditions were applied to an array of olefin substrates (Table 2 and Table S1). Aliphatic alkenes (Table 2, entries 1−3) are converted successfully to their epoxides with retention of the geometry at the olefin. Such stereoretention suggests either (a) concerted O atom transfer from the metal-based oxidant or (b) a stepwise mechanism sufficiently fast to outcompete C−C bond rotation in a radical/cationic intermediate.[5g,10] Additionally, C−Br homolysis is not observed in the reaction of an aliphatic halide (Table 2, entry 4), nor is Baeyer−Villiger oxidation competitive in an unsaturated ketone (Table 2, entry 5). The system is also amenable to the epoxidation of challenging electron-deficient alkenes (Table 2, entries 6 and 7). Even the extremely electron-poor diethyl maleate (Table 2, entry 8), reasonable epoxidation of which is only achieved via the exceptionally electrophilic oxidant HOF,[11] undergoes limited epoxidation with this methodology. Arenes of various functionalities (Table 2, entries 9−13) are compatible as well. The epoxidations of 2- and 4-vinylpyridine (Table 2, entries 11 and 12) are particularly noteworthy, as the ligating nitrogen atoms do not inhibit catalysis and undesired oxidation to the pyridine *N*-oxides is not observed. Transformations of sensitive substrates such as allyl halides (Table 2, entries 14 and 15) and phenyldimethylvinylsilane (Table 2, entry 16) highlight the surprising mildness of this powerful oxidant system. Finally, epoxidation of an unsaturated *N*-hydroxysuccinimide (NHS) ester (Table 2, entry 17) provides not only a bifunctional product but also a route to epoxy amides through subsequent displacement of the activated ester[12] with amines; typically, amides (e.g., Table S1, entry 13) are not directly compatible with metal-based oxidants due to α-C−H oxidation.[13] Other incompatible functional groups include ethers and phenols (Table S1, entries 14 and 15), which are both oxidized nonspecifically, and alcohols (Table S1, entry 16), which are competitively oxidized to carbonyls.

With minor modifications, the methodology is extendable to basic *N*-containing, oxidatively unstable substrates (Table 2, entries 18 and 19). By protecting these functionalities as their BF$_3$ adducts[14] and conducting reactions at −78 °C, good yields of the epoxides are obtained. Furthermore, use of BF$_3$·MeCN as an in situ BF$_3$ source provides the epoxides directly, without the need for a second step to cleave the N−BF$_3$ adducts (see the Supporting Information). In the absence of BF$_3$ protection, oxidative decomposition of these alkenes is observed.

Importantly, the methodology can be efficiently scaled to rapidly produce gram quantities of epoxides. For example, the epoxidation of butyl methacrylate (Scheme 1), carried out on a ~2 g scale, furnished the epoxide in 87% isolated yield. Thus, this protocol also enables synthesis of preparatively useful amounts of epoxides within 5 min in a manner analogous to the small-scale reactions.

Scheme 1. Gram-scale Synthesis of Butyl 2-Methyl-2-oxiranecarboxylate



Intra- and intermolecular competition experiments (Scheme 2) were carried out to interrogate the nature of the active oxidant. Geranyl acetate provided an intramolecular competition (Scheme 2A), as it contains two alkene moieties with similar steric properties but differentiated electronic properties. When subjected to the standard reaction conditions with 1.0 equiv PAA$_M$, a mixture of the 2,3- and 6,7-epoxides, as well as the diepoxide, was obtained in a 1:10:4 ratio, preferring oxidation of the more electron-rich alkene. Conducting the same competition at −78 °C further differentiated the alkenes, yielding a 1:12:3 ratio of products. Similar results were obtained in the intermolecular competition between electron-rich 2,4,4-trimethyl-2-pentene and electron-deficient butyl methacrylate (Scheme 2B). Under standard conditions, the relative reactivity was ca. 5:1 in favor of 2,4,4-trimethyl-2-pentene. Lowering the temperature to −78 °C increased the relative reactivity to 12:1, suggesting this methodology may extend to selective epoxidation of molecules with electronically dissimilar alkenes. The preference for epoxidation of the more electron-rich olefin in these experiments indicates an electrophilic active oxidant, consistent with a high-valent Mn = O species.[15]

The Mn/2-PyCO$_2$H system was compared with related in situ generated oxidation systems Mn/phen and Mn/bipy.[5e] Under this study's standard conditions, Mn/2-PyCO$_2$H dramatically outperforms both Mn/phen and Mn/bipy in the epoxidation of 1-octene, yielding the epoxide in 15−20% greater selectivity (Table 3). Similar results were obtained with comparably electron-rich and electron-poor alkenes (Table S2). It is important to note that the nature of the peracetic acid used to generate the active oxidant is critical, and we therefore chose to compare systems using our PAA$_M$ solution. Conditions used in other studies with respect to the peracetic acid, e.g., as-received commercial PAA,[5c] resin-synthesized PAA,[5d,e] will yield different results with each system (see the Supporting Information for further discussion).

Table 3. Comparison of Mn/2-PyCO$_2$H to Mn/phen and Mn/bipy for Epoxidation of 1-Octene[a]

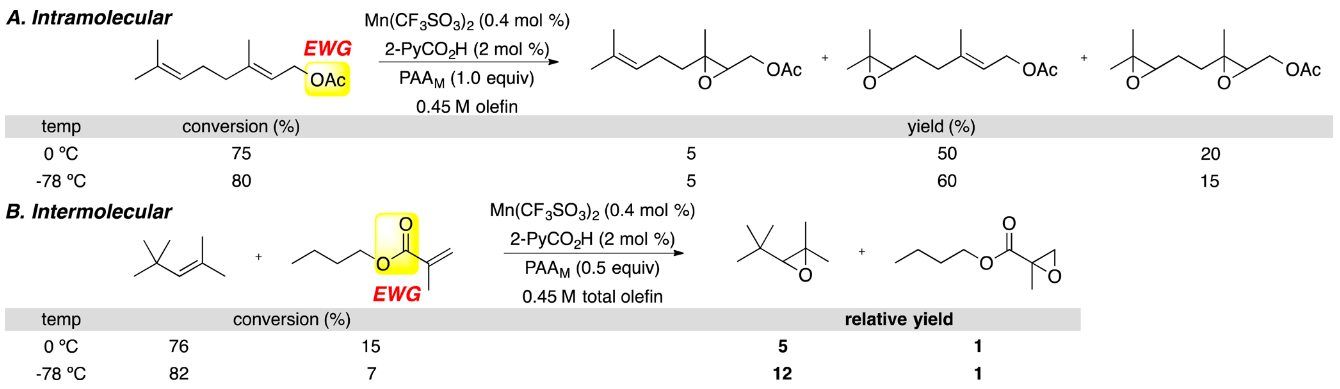
	ligand	conv (%)	yield (selectivity) (%)
1	2-PyCO$_2$H	98	83 (85)
2	phen	54	35 (66)
3	bipy	61	43 (70)

[a] 0.4 mol % of Mn(CF$_3$SO$_3$)$_2$, 2 mol % of ligand, 100 μmol of 1-octene in MeCN (0.45 M), 1.1 equiv of PAA$_M$, 0 °C, 5 min; PAA$_M$ added at a rate of ~5 μL every 10 s. Conversion and yield determined by GC relative to dodecane internal standard. Results are an average of three trials: conversion ± 2%, yield ± 1%.

We hypothesize that the outstanding oxidant efficiency of this system is attributable to both the durability of 2-PyCO$_2$H[6b] and the coordination environment at Mn. Exploration of related ligands (Table 4 and Table S3) suggests this phenomenon is common across a wider family of "picolinic acid-like" ligands; comparable reactivity is observed with 2-pyrimidinecarboxylic acid (Table 4, entry 2), 1-isoquinolinecarboxylic acid (Table 4, entry 3), and 1-methyl-2-imidazolecarboxylic acid (Table 4, entry 4). Ligands not incorporating similar features (Table 4, entries 5−7) do not generate competent catalysts. Further inspection of these ineffective cases illustrates that all aspects of the 2-PyCO$_2$H binding motif are required for catalysis: an aromatic nitrogen donor, a carboxylate[16] donor, and a connectivity capable of forming a five-membered chelate. Of particular interest is the incorporation of an anionic ligand to the coordination sphere, a known paradigm for stabilization of reactive, high-valent metal−oxo complexes.[17]

We have reported an effective oxidant system for olefin epoxidation based on Mn(CF$_3$SO$_3$)$_2$, 2-PyCO$_2$H, and PAA. This method is highlighted by the following characteristics: its ease of use as an in situ generated oxidant system; the simplicity, accessibility, and economy of its components; and its ability to produce preparatively useful quantities of a broad range of epoxides within minutes. The Mn/2-PyCO$_2$H system reported here is further distinguished from related systems[5d,g,i] by its superior oxidant efficiency. This report provides a complement to the work of Browne et al.,[5i] which demonstrated dihydroxylation of electron-deficient olefins using a similar catalyst system. Though their system also shows some epoxidation reactivity—often concomitant with

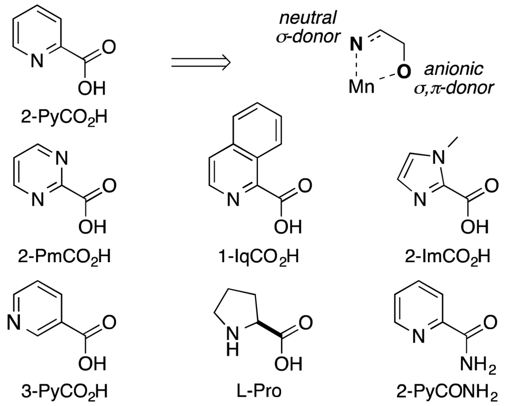
Scheme 2. Competition Experiments with Mn/2-PyCO$_2$H Catalyst System



temp	conversion (%)	yield (%)		
0 °C	75	5	50	20
-78 °C	80	5	60	15

temp	conversion (%)		relative yield	
0 °C	76	15	**5**	**1**
-78 °C	82	7	**12**	**1**

Table 4. Binding Motif of 2-PyCO$_2$H and Expansion of 1-Octene Epoxidation to Related Ligands[a]



	ligand	conv (%)	yield (selectivity) (%)
1	2-PyCO$_2$H	98	83 (85)
2	2-PmCO$_2$H	94	77 (82)
3	1-IqCO$_2$H	91	77 (85)
4	2-ImCO$_2$H[b]	90	71 (79)
5	3-PyCO$_2$H	<10	trace
6	L-Pro	<10	trace
7	2-PyCONH$_2$	<10	trace

[a] 0.4 mol % of Mn(CF$_3$SO$_3$)$_2$, 2 mol % of ligand, 100 μmol of 1-octene in MeCN (0.45 M), 1.1 equiv of PAA$_M$, 0 °C, 5 min. Conversion and yield determined by GC relative to dodecane internal standard. Results are an average of three trials: conversion ± 2%, yield ± 1%. [b] For ligand solubility, reactions were run in 9:1 MeCN/H$_2$O (v/v).

dihydroxylation—the chemically distinct Mn-based active oxidant generated in our system dramatically expands the scope of epoxidation, with complete selectivity for epoxides over diols. Further studies are underway to elucidate the nature of the proposed electrophilic, high-valent Mn = O active oxidant and to advance our understanding of the chemistry underlying the efficiency of this system.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00518.

Experimental procedures, discussion of catalyst speciation, expanded substrate scope, effects of PAA formulation, additional comparisons between catalyst systems, and additional ligand screening trials (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: stack@stanford.edu.

Notes

The authors declare no competing financial interest.

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